(less than one-half an event per month increase). Many women will be unable to tolerate the adverse effects. (Level of Evidence = 1a)

Synopsis

To assemble studies for inclusion, these authors searched three trial registries and 13 electronic databases, including the Cochrane Library, with reference lists of retrieved articles to identify randomized studies. They included studies published in any language. Two researchers independently identified the studies for inclusion; data were extracted by one reviewer and checked by another. They included five published and three unpublished studies that enrolled a total of 5,914 premenopausal and postmenopausal women. The overall study quality was low: many women dropped out, some authors shifted end points mid-study, and some authors used the "last observation carried forward." Benefit was statistically significant but clinically minimal for most outcomes. On average across the studies, treatment, compared with placebo, resulted in one additional satisfying sexual event every two months. Diary scores for sexual desire increased from 1.7 to 2.3 points on a scale of 0 to 84 (four studies), and scores on the female sexual function index increased an average of 0.2 to 0.4 on a scale of 1.2 to 6.0. There was minimal or no change in the women's mean global impression of improvement. Patients who received treatment were twice as likely to drop out because of adverse effects, including dizziness, which was four times more likely in that group.

Study design: Meta-analysis (randomized controlled trial)

Funding source: Self-funded or unfunded

Setting: Various (meta-analysis)

Reference: *Jaspers L, Feys F, Bramer WM, Franco OH, Leusink P, Laan ET. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis.* JAMA Intern Med. *2016;176(4):453-462.*

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Newer Sulfonylureas Not Associated with Increased Mortality, MIs, or Strokes

Clinical Question

Are newer-generation sulfonylureas associated with bad outcomes in patients with type 2 diabetes mellitus?

Bottom Line

In multiple randomized trials, the long-term use of second- or third-generation sulfonylureas in patients with type 2 diabetes is not associated with more deaths, myocardial infarctions (MIs), or strokes. The included trials tended not to report other safety data. (Level of Evidence = 1a)

Synopsis

These authors reviewed two databases and the Cochrane Library to identify randomized trials of second- or third-generation sulfonylureas in patients with type 2 diabetes. Additionally, they searched for unpublished studies by looking at clinical trial registries and the abstracts of international diabetes meetings. The trials had to be at least one year in duration and evaluate all-cause or cardiovascular mortality. If reported in the included study, these authors also collected data on MIs and strokes. Because most of the trials were interested only in nearly meaningless markers of glycemic control, these outcomes were often missing (36 studies representing 10% of the patient pool), so the authors tried to contact the original study team to obtain the missing outcome data (five responded but provided no data). The authors also excluded studies that compared sulfonylureas with drugs that have been withdrawn from the market. Two of the authors independently assessed studies for inclusion and resolved disagreements by consensus, using a third party only when they could not agree. They also assessed each study's potential for bias. Finally, in addition to the usual statistical gymnastics, these authors did a "trial sequential analysis" that allows for the assessment of overall power as well as dampens the potential impact of multiple analyses.

Ultimately, they included 47 trials with approximately 38,000 patients but only 890 deaths. The trials lasted from 12 to 133 months and were generally of decent quality. In the end, the use of newer sulfonylureas was not associated with any statistically significant increase in all-cause mortality, cardiovascular mortality, MI, or stroke. When the authors restricted the analysis to studies that lasted at least two years, they found no difference. Finally, their trial sequential analysis suggested that the data are robust enough to detect at least a 0.5% absolute difference in outcomes, a value that would translate to a number needed to treat to harm of 200.

Study design: Meta-analysis (randomized controlled trial)

Funding source: Government

Setting: Various (meta-analysis)

Reference: *Rados DV, Pinto LC, Remonti LR, Leitão CB, Gross JL. The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials [published correction appears in* PLoS Med. *2016;13(6):e1002091].* PLoS Med. *2016;13(4):e1001992.*

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